PATENT APPLICATION
Attorney Docket No.: QUIG-1082US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Richard A. Rosenbloom	)	
Application No.: 09/847,121	)	Group Art Unit: 1617
Filed: May 2, 2001	)	Examiner: M. Bahar
For: Compositions and Methods for the Treatment of Diabetic Neuropathy	)	

TRANSMITTAL LETTER FOR APPEAL BRIEF

Commissioner for Patents
Washington, D.C. 20231

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DOCKET NO.: QUIG-1002US

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: **Richard Rosenbloom**

Serial No.: **09/847,121** Group Art Unit: **1617**

Filed: **May 2, 2001** Examiner: **Mojdeh Bahar**

For: **COMPOSITIONS AND METHODS FOR THE TREATMENT OF DIABETIC NEUROPATHY**

APPEAL BRIEF

This is an appeal from the Final Rejection dated January 2, 2002 (hereinafter "the Final Rejection"). This appeal brief is timely by virtue of a Notice of Appeal filed on June 2, 2002.

Appellant respectfully submits that the sole remaining rejection in the Final Rejection should be reversed for the reasons set forth below.

I. The Real Party In Interest

The real party in interest is the Quigley Corporation, a corporation based in Doylestown, Pennsylvania.

II. Related Appeals And Interferences

None.

III. The Status Of The Claims

Claims 1-15 are currently pending in the present application. Claims 16-25 have been canceled without prejudice to resubmission. Claims 7-9, 11, and 14 are currently withdrawn from consideration on the basis that claims 7-9, 11 and 14 are drawn to a non-elected species, as set forth by the Examiner at page 3 of the Final Rejection. Claims 1-6, 10, 12-13 and 15 are rejected, and all rejections are appealed. A copy of the claims under appeal is attached hereto as

an appendix.

IV. The Status Of Amendments Filed After Final Rejection

An amendment after final rejection was filed on April 1, 2002, and this amendment was entered for purposes of Appeal as indicated in the Advisory Action dated May 21, 2002.

V. Summary Of The Invention

In general, the invention relates to a composition useful in treating diabetic neuropathy by a method of administration selected from oral administration, parenteral administration and inhalation. Diabetic neuropathy refers to a form of long-term tissue damage, which occurs as a symptom of diabetes. More specifically, diabetic neuropathy refers to long-term damage to nerve tissue in persons afflicted with diabetes. This damage is often associated with other tissue damage, particularly when the nerve damage afflicts the extremities of the patient, since loss of feeling, motor control and/or pain sensation in the extremities frequently leads to other injuries.

The composition of the present invention includes three components, a compound that promotes synthesis of nerve growth factor, an aldose reductase inhibitor and an antioxidant. This particular combination of ingredients provides significant, beneficial results when administered to patients suffering from diabetic neuropathy. Such beneficial effects may include stabilization of the nerve damage, reduction in nerve damage, relief from pain, as well as nerve growth and restoration of at least some feeling or sensation to the afflicted area. It is thought that this combination of ingredients tackles diabetic neuropathy via several different mechanisms which, taken together, provide the aforementioned beneficial effects.

Importantly, the composition of the present invention does not appear to exhibit the severe said effects of many prior art compositions that have been proposed for the treatment of this ailment.

In the broadest claim at issue in this appeal, the composition of the present invention includes an amount of one of vitamin D_3; and the vitamin D_3 derivative 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene,

pharmaceutically acceptable salts thereof and mixtures thereof, effective to promote synthesis of nerve growth factor. This composition also includes an effective amount of an aldose reductase inhibitor and an effective amount of an antioxidant.

As a result of an election of species requirement, examination has been carried out on the elected species, which includes vitamin D_3 as the compound that promotes synthesis of nerve growth factor, quercetin as the aldose reductase inhibitor and ascorbyl palmitate as the antioxidant.

VI. Issue On Appeal

The sole issue to be considered on appeal[1] may be concisely summarized as follows:

Issue 1: Whether claims 1-6, 10, 12-13 and 15 are unpatentable under 35 U.S.C. §103(a) over U.S. Patent No. 5,976,568 to Riley (hereinafter "Riley")?

VII. Grouping Of Claims

For the purpose of the instant appeal, Appellant groups claims 1-6, 10, 12-13 and 15 into one group. Thus, all of claims 1-6, 10, 12-13 and 15 stand or fall together.

[1] In the Advisory Action dated May 21, 2002, the Examiner indicated that the amendment after final rejection filed on April 1, 2002, overcame the rejections to claims 1, 2, and 6 under 35 U.S.C. §112, first paragraph and to claims 1-6, 10, 12-13 and 15 under 35 U.S.C. §112, second paragraph that were raised in the Final Rejection dated January 2, 2002. Thus, the sole remaining rejection is the rejection under 35 U.S.C. §103(a) appealed here.

VIII. Argument – The Rejection And Appellant's Response.

Issue 1: Whether claims 1-6, 10, 12-13 and 15 are unpatentable under 35 U.S.C. §103(a) over U.S. Patent No. 5,976,568 to Riley (hereinafter "Riley").

The Rejection

The relevant portion of the text of the Examiner's rejection of claims 1-6, 10, 12-13 and 15 in the Final Rejection reads as follows:

> "Riley (US 5,976,568) discloses an oral daily supplement composition comprising Vitamins A, D, E, C (Buffered Calcium Ascorbate, Ascorbic acid and Ascorbyl Palmitate) and quercetin, see claim 2. Riley (US 5,976,568) also discloses an oral daily supplement composition comprising vitamins A, C, D3 and E, see claim 3. See also Table II columns 25 and 28.
>
> It would have been obvious to one of ordinary skill in the art at the time the invention was made to employ an amount [e]ffective to promote nerve growth of a vitamin D3 derivative, ascorbyl palmitate and quercetin in a single topical [sic] composition."

In the Advisory Action dated May 21, 2002, the Examiner maintained the above rejection to claims 1-6, 10, 12, 13 and 15. The relevant portion of the Advisory Action is reproduced below.

> "The request for reconsideration has been considered but does NOT place the application in condition for allowance because: Note that claim 2 of Riley discloses an oral daily dosage composition comprising Vitamins A, D, C and quercetin. Tables 2 and 3 further clarify the form of these vitamins, e.g., Vitamin D (D3, Cholecalciferol), Vitamin C (ascorbic acid and ascorbyl palmitate[)]. Note also that the amounts in the instant application are claimed as 'effective amounts' and they are further defined on pages 4, 6 and 7 of the specification. Note that amounts disclosed in Riley (i.e., 400 IU of vitamin D, 0-500 mg of quercetin and 20-1000 mg of vitamin C per day per subject) read on the claimed amounts herein (i.e., 6-14.3 IU/Kg of vitamin D, 13-21.4 mg/Kg of quercetin and 11-28.6 mg/Kg of ascorbyl palmitate[)]. Further note that Modules 1-3 of the present invention may be administered together or in any suitable combination. Intraconversion [sic] of dosage forms and/or simultaneous vs. sequential administration of

compositions comprising the same active is within the purview of the Skilled Artisan and is therefore obvious."

Referring now to the relevant law governing the obviousness rejection in patent examination, MPEP § 2143.03 states that:

> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C 103, then any claim depending therefrom is nonobvious. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1998).

The Claimed Invention

Claim 1 of the present application requires composition comprising a mixture of an amount of a compound that promotes synthesis of nerve growth factor selected from the group consisting of vitamin D_3; 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene; pharmaceutically acceptable salts thereof and mixtures thereof, which is effective when administered in the composition to promote synthesis of nerve growth factor, an amount of an aldose reductase inhibitor which is effective when administered in the composition to inhibit aldose reductase and an effective amount of an antioxidant. The elected species currently under examination is a composition comprising a mixture of an amount of vitamin D_3, which is effective when administered in the composition to promote synthesis of nerve growth factor, an amount of quercetin which is effective when administered in the composition to provide aldose reductase inhibition, and an effective amount of ascorbyl palmitate to act as an antioxidant.

Difference Between a Composition and an Oral Daily Dosage

The Examiner first takes the position that Riley discloses an oral daily supplement composition comprising vitamins A, D, E, C (buffered calcium ascorbate, ascorbic acid and

ascorbyl palmitate) and quercetin in claim 2 of Riley. However, as is clear from the specification of Riley, and especially Example 2 of Riley, the claim 2 of Riley refers to a total daily dosage and not to a specific composition as the Examiner states. This is important because Riley teaches that the total daily dosage of claim 2 should be divided into several distinct modular formulations. See e.g. col. 7, lines 33-39 and col. 20, lines 42+ of Riley. Thus, Riley does not disclose the composition containing vitamins A, D, E, C and quercetin that the Examiner relies upon in support of the rejection. Rather, Riley discloses several distinct compositions referred to as "modules" which are shown in Tables II-III at columns 25-28 and mentioned in claims 3-5 of Riley.

The Skilled Person Would Not Combine Ingredients from Different Modules of Riley

As support for the Examiner's position, the Examiner first states that Modules 1-3 of Riley may be administered together or in any suitable combination. This, however, does not teach a skilled person to make a single composition comprising the ingredients of Modules 1-3. Rather, Riley clearly teaches that Modules 1-3 should be separate and distinct compositions.

The Examiner also takes the position that interconversion of dosage forms and/or simultaneous or sequential administration of compositions comprising the same active is within the purview of the skilled artisan and is therefore obvious. As pointed out above, simultaneous or sequential administration of two different compositions, i.e. Modules 1 and 3 for example, does not result in the provision of a composition of the present invention. Rather, it results in the provision of two distinct, separate compositions, namely, Modules 1 and 3, as is clearly taught by Riley.

Although the Examiner's position is not entirely clear on this point, it appears that the Examiner is also alleging that it a skilled person would, using common general knowledge, combine ingredients from different Modules of Riley to arrive at the present invention.[2] However, the Examiner has not provided any reason, motivation or suggestion to select the specific ingredient, i.e. quercetin, and combine that ingredient with the composition of another

[2]This appears to be what the Examiner means by "interconversion of dosage forms."

Module in order to arrive at the present invention. There are lots of different ingredients disclosed in the Modules of Riley and the skilled person, if he were mixing ingredients, would have no motivation to pick quercetin from among the other ingredients.

More importantly, however, the Examiner overlooks several important teachings of Riley that directly contradict the conclusion that it would be obvious for a skilled person to mix the ingredients of different Modules of Riley. Specifically, Riley points out at col. 3, lines 8-15 that currently available multi-vitamin formulations are designed without consideration for micronutrient interactions. Riley then goes on to say that, "The novel formulations presented in accordance with the present invention provide the right amount of the right micronutrients at the right time to avoid and overcome the problems commonly seen with vitamin supplementation today." Col. 5, lines 22-26 of Riley. Riley also points out that,

> "The unique and original vitamin and mineral Module 1 formulation system of the present invention is further based on criteria not previously considered such as:
> 1. vitamin-vitamin interactions, (See Appendix A)
> 2. vitamin-mineral interactions;..."

See col. 10, lines 46-51 of Riley. Riley even conducted studies to determine if there were adverse or positive interactions between various components of some of the formulations. See col. 17, lines 21-29 of Riley.

From the foregoing, it is absolutely clear that a skilled person, upon reading Riley, would not mix ingredients from one Module with ingredients from another Module since Riley clearly teaches that the various Modules were specifically selected to avoid interactions between vitamins and/or minerals in the compositions.

Riley also provides a second reason not to combine ingredients from different modules, namely to take into account factors such as loss of water-soluble nutrients during the day. See e.g. col. 3, lines 17-22. Riley's modular formulations are also specially designed to account for this factor. See item 4 of the list at col. 10, lines 46-64 of Riley. Therefore, the skilled person would expect that combining ingredients from the different modules of Riley, as the examiner suggests would be detrimental to the performance of the formulations for at least these two reasons and thus would be inclined

to avoid combining ingredients from different formulations.

Numerous Modifications Must be Made to the Oral Daily Dosage of Claim 2 of Riley

The total daily dosage range of claim 2 of Riley differs from the elected species of the present application in at least the following respects:

1. Claim 2 does not mention vitamin D_3;
2. quercetin is an optional ingredient of the composition of claim 2 since it may be present in an amount of 0.0 to 500 mg;
3. claim 2 does not mention ascorbyl palmitate; and
4. claim 2 does not specify an amount for ascorbyl palmitate.

Accordingly, the skilled person starting from the oral daily dosage of claim 2 of Riley must take the following steps to arrive at the elected species of the present invention:

1. select the particular form of vitamin D claimed in the claims of the present application;
2. select an amount of the particular form of vitamin D which is effective to promote synthesis of nerve growth factor;
3. decide to include quercetin or another aldose reductase inhibitor as an ingredient in the composition;
4. select an amount of quercetin or another aldose reductase inhibitor which is effective to act as an aldose reductase inhibitor;
5. select ascorbyl palmitate as an appropriate form of vitamin C for inclusion in the composition; and
6. select an amount of ascorbyl palmitate that is effective to act as an antioxidant.

For each of these six steps, the Examiner must provide some teaching or motivation in Riley to make the necessary selection of ingredients and amounts in order to modify the

composition of Riley to arrive at the composition claimed in the present application. *In re Linter*, 458 F.2d 1013, 1016, 173 USPQ 560, 562 (CCPA 1972); *In re Fine*, 837 F.2d, 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Riley does not provide the required teachings or motivation for the skilled person to carry out any of the foregoing six steps, and certainly does not provide sufficient teachings to make all six modifications required to arrive at the present invention.

Specifically, based on the disclosure of claim 2 of Riley, the skilled person has no reason to pick the specific form of vitamin D claimed in the present claims. Rather, claim 2 only gives a generic disclosure of vitamin D and there are many forms of vitamin D, which are not included in the present claims. Thus, the skilled person has no motivation to select, for example, vitamin D_3 as the Examiner suggests.

The Examiner apparently relies on the Examples of Riley to provide a motivation to select vitamin D_3 as the appropriate form of vitamin D to employ in the daily dosage of claim 2. However, it is important to note that Riley clearly avoids a combination of quercetin with vitamin D_3 in all of its examples. More specifically, in both versions of Modules 2, 5 and 6, and all four versions of Module I shown in Tables II-III of Riley, vitamin D_3 is employed and quercetin is always purposely left out of the composition. Then, in all four versions of Module 3 and both versions of Module 7, quercetin is employed, but vitamin D_3 is purposely left out. In fact, sixteen compositions disclosed in Riley include one of vitamin D_3 or quercetin, but not a single composition in Riley includes a combination of both of these compounds as is required by the claims of the present application. From these numerous examples, the skilled person would clearly be led not to include quercetin and vitamin D_3 in the same composition, especially in view of the fact that Riley clearly teaches that the ingredients of the various modules were carefully selected to avoid vitamin and/or mineral interactions as discussed above. Furthermore, none of the Examples of Riley teaches or suggests a combination of quercetin, ascorbyl palmitate and vitamin D_3.

The Examiner has also failed provide any evidence that the skilled person using the teachings of Riley would select an amount of vitamin D_3 effective to promote the synthesis of

nerve growth factor or an amount of quercetin effective to act as an aldose reductase inhibitor. Riley does not mention either the desirability of using vitamin D_3 to promote the synthesis of nerve growth factor or the desirability of using quercetin as an aldose reductase inhibitor. Thus, the skilled person has no basis in the teachings of Riley to arrive at these respective effective amounts since the functions of these materials in the claimed composition is not even disclosed in Riley.

Further, the Examiner apparently bases the conclusion that the vitamin C of claim 2 of Riley is "buffered calcium ascorbate, ascorbic acid and ascorbyl palmitate" on the Examples in Tables II-III of Riley. However, Riley nowhere discloses the quantity of ascorbyl palmitate, which is employed nor does claim 2 of Riley indicate anywhere that the vitamin C should include ascorbyl palmitate. Thus, the skilled person when starting with Example 2 of Riley, must first decide to use vitamin C in the form of ascorbyl palmitate. This is not as straightforward as it may first appear since the skilled person, reading the Examples of Riley, has at least seven different options, namely, buffered calcium ascorbate, ascorbic acid, ascorbyl palmitate, a mixture of buffered calcium ascorbate and ascorbic acid, a mixture of buffered calcium ascorbate and ascorbyl palmitate, a mixture ascorbic acid and ascorbyl palmitate, and a mixture of buffered calcium ascorbate, ascorbic acid and ascorbyl palmitate. Moreover, other forms of vitamin C are known to persons skilled in the art.

More importantly, however, the skilled person must take the further step of deciding to use a sufficient amount of ascorbyl palmitate to provide an antioxidant effect, in order to arrive at the present invention. Since Riley nowhere discloses the amount of ascorbyl palmitate that should be employed, there is no basis whatsoever in Riley for reaching the conclusion that it would be obvious to employ the amount of ascorbyl palmitate required by the claims of the present application.

Riley Does Not Disclose An Effective Amount of an Aldose Reductase Inhibitor

In addition, the broadest quercetin dosage range disclosed by Riley is 0-500 mg per day. However, the only evidence in the record as to what is an effective amount of an aldose reductase

inhibitor is found in the present application, which indicates that an effective amount of aldose reductase inhibitor (e.g. quercetin) may be 13-21.4 mg/Kg body weight daily (see p.6, lines 24-26). This translates into about 975–1605 mg/day for a typical 75 kg adult. From this, the skilled person would draw the conclusion that Riley does not appear to employ an amount of quercetin that would be effective to provide aldose reductase inhibition in accordance with the present invention since the upper limit of the Riley range is only about half the amount disclosed in the present specification for a typical 75 kg adult.

The Examiner may be taking the position that taking the upper limit of Riley, i.e. 500 mg per day of quercetin, and administering this to a 30 kg person would bring the teachings of Riley within the scope of an effective amount, as claimed. However, this position would be unrealistic in view of the common general knowledge of a skilled person. For example, the skilled person is aware that dosage levels should be related to body weight. See e.g. the U.S. Food and Drug Administration Protocol for the Conduct of Non-Clinical Laboratory Studies, 21 C.F.R. §58.120 and the U.S. Food and Drug Administration Redbook 2000 IV.C.9.b Toxicological Principles for the Safety of Food Ingredients which says that body weight should be measured daily or at least every three days when doing toxicology studies.

The importance of this is that a skilled person, when reading the range of Riley, would conclude that the upper limit of the range is to be employed only for persons with body weights at the upper limit of the body weight range and that lesser dosages should be applied for persons with lower body weights. The reasons for this are twofold. First, lower body weight generally means that a lower dosage is required to achieve the same effect. Second, as the ratio of dosage to body weight increases, toxicity would be expected to increase thereby increasing the risk to the patient. As a result, the skilled person would not interpret the teachings of Riley as suggesting that a person of well below average body weight, i.e. about 35 Kg, should receive the maximum disclosed dosage of quercetin, i.e. 500 mg/day. Thus, a reasonable reading of the teachings of Riley leads to the conclusion that Riley does not disclose an effective amount of quercetin to act as an aldose reductase inhibitor.

Accordingly, the evidence of record indicates that Riley does not disclose the limitation

of the claims of the present application, which requires "an amount...which is effective...to provide aldose reductase inhibition."

Numerous Modifications Must be Made to the Oral Daily Dosage of Claim 2 of Riley

The Examiner also relies on the compositions of claim 3 and Table II of Riley in support of this rejection. First, the two separate oral dosage compositions of claim 3 of Riley are the same as the AM and PM Modules 1 of Table II of Riley. In order to arrive at the present invention starting from these compositions of Riley, a skilled person would have to make the following modifications:

1. select an amount of vitamin D_3 or another compound which promotes synthesis of nerve growth factor, which is effective to promote synthesis of nerve growth factor;
2. decide to include quercetin or another aldose reductase inhibitor, as an ingredient in the composition (claim 3 of Riley does not mention quercetin and the compositions of Table II of Riley never include quercetin in the same composition as vitamin D_3);
3. select an amount of quercetin or another aldose reductase inhibitor which is effective to act as an aldose reductase inhibitor;
4. select ascorbyl palmitate as an appropriate form of vitamin C for inclusion in the composition (claim 3 of Riley does not mention ascorbyl palmitate); and
5. select an amount of ascorbyl palmitate that is effective to act as an antioxidant.

The Examiner has provided no teaching or suggestion in Riley to make any one of the five modifications listed above, and certainly no teachings to make all five modifications, nor has the Examiner provided any evidence that the amount of vitamin D_3 employed in claim 3 of Riley is an amount effective to promote the synthesis of nerve growth factor, as discussed above with respect to the Examiner's rejection based on the oral daily dosage of claim 2. In addition, to the extent that the Examiner has taken the position that it is within the purview of the skilled person to make these modifications, these arguments have been addressed in detail above in the section

entitled, "The Skilled Person Would Not Combine Ingredients from Different Modules of Riley."

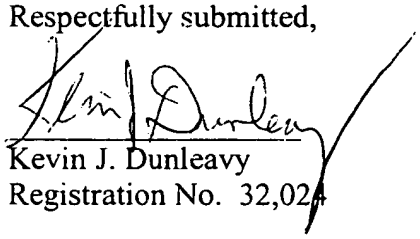
Since claims 2-6, 10, 12-13 and 15 all depend from claim 1, these claims are patentable for the same reasons as claim 1 given above. See *In re Fine*, cited *infra*.

With respect to the subject matter of claims 1-6, 10, 12, 13 and 15, taken as a whole, i.e. not limited to the elected species, these claims are clearly unobvious over Riley for the same reasons as are given above with respect to the elected species. Riley does not teach or suggest any composition, which includes both vitamin D_3 and quercetin, and Riley teaches away from combining these two ingredients in a single composition. Moreover, Riley does not provide the motivation to make any of the modifications of the various compositions disclosed in Riley which are required to arrive at the present invention as claimed in claims 1-6, 10, 12-13 and 15, as discussed above. Accordingly, for these reasons, Appellant submits that the rejections to claims 1-6, 10, 12, 13 and 15 under 35 U.S.C. §103(a) were made in error and requests the Examiners-in-chief reverse the rejections. Therefore, for at least these reasons, claims 1-6, 10, 12, 13 and 15 is considered to unobvious over Riley and Appellant respectfully requests that the final rejection to claims 1-6, 10, 12, 13 and 15 be reversed.

IX. Conclusion

For the foregoing reasons, Appellant respectfully submits that the sole remaining rejection should be reversed, and all claims allowed, and such a decision is respectfully solicited.

Respectfully submitted,



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APPENDIX- CLAIMS ON APPEAL

1. A composition for the treatment of diabetic neuropathy by a method of administration selected from the group consisting of oral administration, parenteral administration and inhalation, the composition comprising a mixture of an amount of a compound that promotes synthesis of nerve growth factor selected from the group consisting of vitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, pharmaceutically acceptable salts thereof and mixtures thereof, which is effective when administered in the composition to promote synthesis of nerve growth factor, an amount of an aldose reductase inhibitor which is effective when administered in the composition to inhibit aldose reductase and an effective amount of an antioxidant.

2. A composition as claimed in claim 1, wherein the compound that promotes the synthesis of nerve growth factor is selected from the group consisting of: vitamin D_3, 1(S), 3(R)-dihydroxy-20(R)-(1-ethoxy-5-ethyl-5-hydroxy-2-heptyn-1-yl)-9, 10-seco-pregna-5(Z), 7(E), 10 (19)-triene, and mixtures thereof.

3. A composition as claimed in claim 1, wherein the aldose reductase inhibitor is selected from the group consisting of: flavonoids, flavonoid derivatives which exhibit aldose reductase inhibiting properties, pharmaceutically acceptable salts thereof and mixtures thereof.

4. A composition as claimed in claim 3, wherein the aldose reductase inhibitor is selected from the group consisting of: (-)-epigallocatechin; (-)-epigallocatechin-gallate; 1,2,3,6-tetra-o-gallyol-β-d-glucose; 2'o-acetylacetoside; 3,3',4-tri-o-methyl-ellagic acid; 6,3',4'-trihydroxy-5,7,8-trimethoxyflavone; 6-hydroxy-luteolin; 6-hydroxykaempferol-3,6-dimethyl ether; 7-o-acetyl-8-epi-loganic acid; acacetin; acetoside; acetyl trisulfate quercetin; amentoflavone; apiin; astragalin; avicularin; axillarin; baicalein; brazilin;

brevifolin carboxylic acid; caryophyllene; chrysin-5,7-dihydroxyflavone; chrysoeriol; chrysosplenol; chrysosplenoside-a; chrysosplenoside-d; cosmosiin; δ-cadinene; dimethylmussaenoside; diacerylcirsimaritin; diosmetin; dosmetin; ellagic acid; ebinin; ethyl brevifolin carboxylate; flavocannibiside; flavosativaside; genistein; gossypetin-8-glucoside; haematoxylin; hispiduloside; hyperin; indole; iridine; isoliquiritigenin; isoliquiritin; isoquercitrin; jionoside; juglanin; kaempferol-3-rhamnoside; kaempferol-3-neohesperidoside; kolaviron; licuraside; linariin; linarin; lonicerin; luteolin; luetolin-7-glucoside; luteolin-7-glucoside; luetolin-7-glucoronide; macrocarpal-a; macrocarpal-b; macrocarpal-d; macrocarpal-g; maniflavone; methy scutellarein; naringenin; naringin; nelumboside; nepetin; nepetrin; nerolidol; oxyayanin-a; pectolinarigenin; pectolinarin; quercetagetin; quercetin; quercimertrin; quercitrin; quercitryl-2'' acetate; reynoutrin; rhamnetin; rhoifolin; rutin; scutellarein; sideritoflavone; sophoricoside; sorbarin; spiraeoside; trifolin; vitexin; wogonin; pharmaceutically acceptable salts thereof, and mixtures thereof.

5. A composition as claimed in claim 3, wherein the aldose reductase inhibitor comprises at least one compound selected from the group consisting of: quercetin, quercetrin, myricetin, kaempferol and myrecetrin.

6. A composition as claimed in claim 1, wherein the antioxidant comprises at least one compound selected from the group consisting of: ascorbyl palmitate, ascorbic acid, vitamin A, vitamin E acetate, α-lipoic acid, coenzyme Q10, glutathione, catechin, galangin, rutin, luteolin, morin, fisetin, silymarin, apigenin, gingkolides, hesperitin, cyanidin, citrin, derivatives thereof which exhibit antioxidant activity, and pharmaceutically acceptable salts thereof.

10. A composition as claimed in claim 1, wherein the antioxidant comprises ascorbyl palmitate.

12. A composition as claimed in claim 5, wherein the compound that promotes the synthesis of nerve growth factor comprises vitamin D_3.

13. A composition as claimed in claim 12, wherein the antioxidant comprises at least one compound selected from the group consisting of vitamin A, vitamin E, and ascorbyl palmitate.

15. A composition as claimed in claim 1, further comprising an effective amount of a pharmaceutically acceptable carrier